IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of: Paul Stark et al.	:	Confirmation No.: 6126
Application No.: 10/814,293	:	Group Art Unit: 1609
Filed: April 1, 2004	:	Examiner: Jeffrey T. Palenik
For: MULTIPARTICULATE BISOPROLOL FORMULATION	:	

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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APPEAL BRIEF

Sir:

Appellants submit this Appeal Brief in furtherance of the Notice of Appeal dated May 26, 2009, Appellants request consideration in view of the following amendments and remarks.

The fees required under 37 C.F.R. § 1.17(h) are paid along with the accompanying TRANSMITTAL OF APPEAL BRIEF. Commissioner is hereby authorized to charge any fees in connection with this appeal, or with any other related matters before the PTO, to the undersigned's Deposit Account No. 50-1943.

I. REAL PARTY IN INTEREST

The real party in interest hereto is the Assignee, Circ Pharma Research and Development, Ltd, a corporation having a place of business at 45 Fitzwilliam Square, Dublin 2, Ireland.

II. RELATED APPEALS AND INTERFERENCES

Appellants or the Assignee are not aware of any related appeals and/or interferences.

III. STATUS OF CLAIMS

Claims 1-32 are currently rejected, as evidenced by the Final Office Action dated November 26, 2008 (Exhibit A).

IV. STATUS OF AMENDMENTS

The amendments to the claims submitted in the Response of February 26, 2009 have not been entered.

The Supplemental Reply filed on April 27, 2009 was not entered.

The Amendment Pursuant to 37 C.F.R. § 41.33 filed concurrently herewith to cancel claims 10-14 has not yet been acted upon by the Examiner.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The instant invention is drawn to a multiparticulate bisoprolol formulation for once-daily oral administration, wherein each particle includes a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating that includes at least one enteric polymer coating material selected from cellulose acetate phthalate, cellulose acetate trimaletate, hydroxyl propyl methylcellulose phthalate, polyvinyl acetate phthalate, Eudragit poly acrylic acid, Eudragit S, Eudragit L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate and shellac; the polymeric coating being effective to achieve an initial lag of bisoprolol release in vivo of at least 4-6 hours following administration and thereafter maintaining therapeutic concentrations of bisoprolol for the remainder of the twenty-four hour period, support for which is found at Page 3, Lines 1-7; Page 8, Line 20 – Page 9, Line 1; Page 23, Line 5 – Page 25, Table 1; Page 39, Line 10 – Page 42, Line 10.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 1-32 are unpatentable under 35 U.S.C. § 103(a) over U.S. Patent No. 5,137,733 to Noda et al. ("Noda et al.") (Exhibit B) in view of U.S. Patent No. 5,580,578 to Oshlack et al. ("Oshlack et al.") (Exhibit C).

B. Whether claims 1-32 are unpatentable under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

VII. ARGUMENT

A. Claims 1-32 are not obvious in view of the combination of Noda et al. and Oshlack et al.

Claims 1-9 and 15-32

Claims 1-9 and 15-32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,137,733 to Noda et al. in view of U.S. Patent No. 5,580,578 to Oshlack et al. Appellants' claimed formulation is a multiparticulate bisoprolol formulation wherein each particle comprises a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating that includes at least one enteric polymer coating material selected from cellulose acetate phthalate, cellulose acetate trimaletate, hydroxyl propyl methylcellulose phthalate, polyvinyl acetate phthalate, Eudragit poly acrylic acid, Eudragit S, Eudragit L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate and shellac. Appellants emphasize that independent claim 1 recites enteric (e.g. pH-dependent) polymers.

Noda et al. does not disclose or suggest a bisoprolol formulation that includes at least one enteric polymer coating material selected from the group recited in claim 1. Noda et al. is limited to pH-independent coatings and makes clear that its formulations are designed for dissolution that is independent of the pH. See, for example, the Abstract ("dissolution pattern irrespective of the pH of a dissolution medium") and the Background of the Invention ("An object of this invention . . . and the rate of the dissolution of the medicinal compound does not depend on the pH of a medium for the dissolution"). The polymers that Noda et al. exemplifies are recognized in the art as pH-

independent. Also, the experiments described in Noda et al. show a formulation that exhibits a pH-independent drug release profile. Clearly, pH-independence is at the very heart of the Noda et al. teaching.

The Office Action indicates that "acrylic polymers are taught [by Noda et al.] at col. 2, lines 40-59 and include Eudragit RS as well as a combination of Eudragit RS and RL." (Exhibit A, Office Action, page 6). However, the acrylic polymers recited by Noda et al. at col. 2, lines 40-59 are polymers that include a trimethylammoniumethyl group in the molecule. (See Exhibit B, Noda et al. at col. 2, line 43). The present claims do not recite acrylic polymers that include a trimethylammoniumethyl group. According to the authoritative reference, "Handbook of Pharmaceutical Excipients," Second Edition, (Eds. A. Wade and P. Weller), p. 363 (1994) (Exhibit D)[1], Eudragit RS and RL are methacrylate copolymers with trimethylammonioethyl functional groups that provide "pH-independent permeability of the polymers."

The present invention, on the other hand, relies on the use of a polymer system for which the dissolution depends on the pH of the medium. Appellants' claimed invention is specifically formulated to exhibit a release of bisoprolol that is affected by the pH of the medium. This is very clearly different from the formulation disclosed by Noda et al. Replacing the pH-independent coatings of Noda et al. with the pH-dependent coatings claimed in the present application would change the principle of operation of the Noda et al. pH-independent formulations. According to M.P.E.P. 2143.01(VI), "If the proposed

[1] This publication is submitted solely as an authoritative reference in accordance with 37 C.F.R. § 41.37(c)(1)(vii), which, according to M.P.E.P. 1205.02, "emphasizes that all arguments and authorities which an appellant wishes the Board to consider should be included in the brief." A copy of this reference is provided herewith as Exhibit D in accordance with M.P.E.P. 1205.02, which states, "If in his or her brief, appellant relies on some reference, he or she is expected to provide the Board with a copy of it in the evidence appendix of the brief."

modification . . . of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious."

Oshlack et al. does not cure the deficiencies of Noda et al. The Office Action relies on Oshlack et al. for its purported disclosure of "a controlled release formulation wherein a barrier layer is incorporated between the medicinal core and the acrylic coating layer." (Exhibit A, Office Action, page 9). Even assuming Oshlack et al. does disclose such a barrier, this does not guide one of skill in the art to a pH-dependent polymer system as presently claimed. Thus, the combination of Noda et al. with Oshlack et al. does not teach or suggest the presently claimed invention. Therefore, Appellants respectfully submit that claims 1-9 and 15-32 are not obvious in view of the combination of Noda et al. and Oshlack et al.

Claims 10-14

Claims 10-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,137,733 to Noda et al. in view of U.S. Patent No. 5,580,578 to Oshlack et al. Appellants seek to simplify the issues on appeal and request entry of the amendment to cancel claims 10-14, which would render the rejection of claims 10-14 moot.

B. Claims 1-32 are not indefinite under 35 U.S.C. § 112, second paragraph.

1. Claim 1 does not recite a narrow limitation within a broad recitation.

Claims 1-9 and 15-32

Claims 1-9 and 15-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action notes that "claim 1 recites the broad recitation 'Eudragit poly acrylic acid,' and the claim also recites 'Eudragit S and Eudragit L' which are narrower statements of the range/limitation." (Exhibit A, Office Action, page 10). Appellants note that claim 1 recites "at least one enteric polymer coating material" prior to the listing of polymers that includes Eudragit poly acrylic acid, Eudragit S, and Eudragit L. (Emphasis added). According to the "Handbook of Pharmaceutical Excipients," p. 365 (Exhibit D), Eudragit S and Eudragit L are the only enteric Eudragit poly acrylates. The inclusion of enteric "Eudragit poly acrylic acid" in claim 1 is merely redundant of the "Eudragit S" and "Eudragit L" recitations and thus clearly sets forth the metes and bounds of the patent protection desired. Therefore, Appellants respectfully submit that claims 1-9 and 15-32 are not indefinite under 35 U.S.C. § 112, second paragraph.

Claims 10-14

Claims 10-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Appellants seek to simplify the issues on appeal and request entry of the amendment to cancel claims 10-14, which would render the rejection of claims 10-14 moot.

2. The recitation of the trademark "Eudragit" does not result in uncertain claim scope.

Claims 1-9 and 15-32

Claims 1-9 and 15-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action states that:

> Claim 1 contains the trademark/trade name 'Eudragit®.' . . . . The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name.

(Exhibit A, Office Action pages 10-11).

However, M.P.E.P. 2173.05(u) states, "The presence of a trademark or trade name in a claim is not, *per se*, improper under 35 U.S.C. 112, second paragraph, but the claim should be carefully analyzed to determine how the mark or name is used in the claim." Claim 1 recites "at least one enteric polymer coating material" and includes in this listing "Eudragit poly acrylic acid", "Eudragit S", and "Eudragit L." These recitations of the term "Eudragit®" in claim 1 are meant to identify a specific source (e.g. manufacturer) recognizable by one of skill in the art for the enteric polymer coating material and enteric poly acrylic acid. The "Eudragit®" class of polymers available from the manufacturer is set forth and classified in the "Handbook of Pharmaceutical Excipients" (Exhibit D), an authoritative reference for those of skill in the art. Exhibit D clearly sets forth the fixed and definite chemical names and properties of the "Eudragit®" class of polymers. The terms "Eudragit poly acrylic acid", "Eudragit S", and "Eudragit L" are used in claim 1 to identify a specific manufacturer of the enteric polymer coating material and enteric poly acrylic acid, whose polymers are given fixed and definite meanings by the manufacturer.

For the foregoing reasons, Appellants respectfully submit that claims 1-9 and 15-32 are not indefinite under 35 U.S.C. § 112, second paragraph.

Claims 10-14

Claims 10-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Appellants seek to simplify the issues on appeal and request entry of the amendment to cancel claims 10-14, which would render the rejection of claims 10-14 moot.

CONCLUSION

Appellants respectfully submit that for at least these reasons the pending claims are valid and favorable reconsideration is earnestly solicited.

The USPTO is authorized to charge Deposit Account No. 50-1943 for any charges in connection with this matter.

Date: July 27, 2009

Respectfully submitted,

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X. CLAIMS APPENDIX

1. A multiparticulate bisoprolol formulation for once-daily oral administration, each particle comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating, said coating comprising at least one enteric polymer coating material selected from the group consisting of cellulose acetate phthalate, cellulose acetate trimaletate, hydroxyl propyl methylcellulose phthalate, polyvinyl acetate phthalate, Eudragit poly acrylic acid, Eudragit S, Eudragit L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate and shellac; said polymeric coating being effective to achieve an initial lag of bisoprolol release in vivo of at least 4-6 hours following administration and thereafter maintaining therapeutic concentrations of bisoprolol for the remainder of the twenty-four hour period.

2. A multiparticulate bisoprolol formulation according to claim 1, wherein the polymeric coating is effective to prevent quantifiable bisoprolol plasma concentrations in vivo for a period of at least 3-6 hours.

3. A multiparticulate bisoprolol formulation according to claim 1, which contains a pharmaceutically acceptable salt of bisoprolol.

4. A multiparticulate bisoprolol formulation according to claim 3, wherein the salt is bisoprolol hemifumarate.

5. A multiparticulate bisoprolol formulation according to claim 1, which has an in vitro dissolution profile which when measured in a U.S. Pharmacopoeia 2 Apparatus (Paddles) in phosphate buffer at pH 6.8 at 37°C. and 50 rpm substantially corresponds to the following: (a) from 0% to 10% of the total bisoprolol is released after 2 hours of

measurement in said apparatus, (b) from 0% to 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and (c) greater than 50% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

6. A multiparticulate bisoprolol formulation according to claim 1, which has an in vitro dissolution profile which when measured in a U.S. Pharmacopoeia 1 Apparatus (Baskets) at 37°C. and 50 rpm in 0.01 N HCl for the first 2 hours followed by transfer to phosphate buffer at pH 6.8 for the remainder of the measuring period substantially corresponds to the following: (a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus; (b) less than 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and (c) greater then 20% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

7. A multiparticulate bisoprolol formulation according to claim 1, wherein a sealant or barrier layer is applied to the core prior to the application of the polymeric coating.

8. A multiparticulate bisoprolol formulation according to claim 7, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.

9. A multiparticulate bisoprolol formulation according to claim 1, wherein the bisoprolol active ingredient is applied to a non-pareil seed having an average diameter in the range of 0.4-1.1 mm.

10. A multiparticulate bisoprolol formulation according to claim 1, wherein the polymeric coating contains a major proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of low permeability.

11. A multiparticulate bisoprolol formulation according to claim 1, wherein the polymeric coating contains a minor proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of high permeability.

12. A multiparticulate bisoprolol formulation according to claim 10, wherein in the or each polymer is a methacrylic acid co-polymer.

13. A multiparticulate bisoprolol formulation according to claim 10, wherein the or each polymer is an ammonio methacrylate co-polymer.

14. A multiparticulate bisoprolol formulation according to claim 12, wherein a mixture of said polymers is used.

15. A multiparticulate bisoprolol formulation according to claim 1, wherein the polymeric coating includes one or more soluble excipients so as to increase the permeability of the coating.

16. A multiparticulate bisoprolol formulation according to claim 15, wherein the or each soluble excipient is selected from a soluble polymer, a surfactant, an alkali metal salt, an organic acid, a sugar and a sugar alcohol.

17. A multiparticulate bisoprolol formulation according to claim 15, wherein the soluble excipient is selected from polyvinyl pyrrolidone, polyethylene glycol and mannitol.

18. A multiparticulate bisoprolol formulation according to claim 15, wherein the soluble excipient is used in an amount of from 1% to 10% by weight, based on the total dry weight of the polymer.

19. A multiparticulate bisoprolol formulation according to claim 1, wherein the polymeric coating includes one or more auxiliary agents selected from a filler, a

plasticiser and an anti-foaming agent.

20. A multiparticulate bisoprolol formulation according to claim 1, wherein the coating polymer is coated to 10% to 100% weight gain on the core.

21. A multiparticulate bisoprolol formulation according to claim 1, wherein the coating polymer is coated to 25% to 70% weight gain on the core.

22. A multiparticulate bisoprolol formulation according to claim 1, wherein a sealant or barrier layer is applied to the polymeric coating.

23. A multiparticulate bisoprolol formulation according to claim 22, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxpropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.

24. An oral dosage form containing a multiparticulate bisoprolol formulation according to claim 1, which is in the form of caplets, capsules, particles for suspension prior to dosing, sachets or tablets.

25. An oral dosage form according to claim 24, which is in the form of tablets selected from disintegrating tablets, fast dissolving tablets, effervescent tablets, fast melt tablets and mini-tablets.

26. A multiparticulate bisoprolol formulation of claim 1, wherein the bisoprolol comprises the (S)-enantiomer of bisoprolol.

27. A multiparticulate bisoprolol formulation of claim 2, wherein the bisoprolol comprises the (S)-enantiomer of bisoprolol.

28. A multiparticulate bisoprolol formulation of claim 3, wherein the bisoprolol salt comprises the (S)-enantiomer of bisoprolol.

29. A multiparticulate bisoprolol formulation of claim 4, wherein the bisoprolol

hemifumarate comprises the (S)-enantiomer of bisoprolol.

30. A multiparticulate bisoprolol formulation of claim 6, wherein the bisoprolol comprises the (S)-enantiomer of bisoprolol.

31. A multiparticulate bisoprolol formulation of claim 26 comprising about 1, 1.25, 2, 2.5, 3, 3.75, 4, 5, 7.5, 10, or 15mg of (S)-bisoprolol.

32. A multiparticulate bisoprolol formulation of claim 31 comprising about 1.25, 2.5, 5, or 7.5mg of (S)-bisoprolol.

IX. EVIDENCE APPENDIX

Exhibit A – Final Office Action dated November 26, 2008.

Exhibit B – U.S. Patent No. 5,137,733 to Noda et al.

Exhibit C – U.S. Patent No. 5,580,578 to Oshlack et al.

Exhibit D – "Handbook of Pharmaceutical Excipients," Second Edition, (Eds. A. Wade and P. Weller), pp. 362-66 (1994).

X. RELATED PROCEEDINGS APPENDIX

None.